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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,126	02/22/2002	Gerald W. DeVries	P-AR 4951	8539

51957 7590 08/26/2005

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,126	DEVRIES, GERALD W.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-40 and 45-57* is/are rejected.

7)☒ Claim(s) *41-44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/7/05 has been entered.

2. Claims 39-57 are pending and are being acted upon in this Office Action.

3. Claim 40 is objected to because "binds the" should have been "binds to the".

4. Claim 41 is objected to because "selected form" should have been "selected from the group consisting of".

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 39-40 and 45-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of extending corneal graft survival following corneal transplantation in a patient comprising administering to said patient an effective amount of a pharmaceutical composition comprising a vascular endothelial growth factor receptor-3 kinase inhibitor selected from the group consisting of 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) and 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51), (2) The said method further comprising administering to said patient an anti-angiogenic agent or an immunosuppressive agent, **does not** reasonably provide enablement for a method of extending corneal graft survival following corneal transplantation in any patient comprising administering to said patient an effective amount of a pharmaceutical composition comprising (1) *any* "VEGFR-3 kinase inhibitor", whereby lymphagiongenesis is suppressed in the cornea of said patient, (2) *any* VEGFR-3 kinase inhibitor" that binds to theVEGFR-3 catalytic

domain, (3) the said method further comprises administering any anti-angiogenic agent, and/or (4) *any* immunosuppressive agent, wherein the pharmaceutical composition is administered prior to, or subsequent to corneal transplantation, two or more times, over a period of at least one or six months as set forth in claims 39-40, and 45-57. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only three VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structures as shown on page 56 and a method of extending corneal graft survival in a rat model of karetoplasty following corneal transplantation by administering a pharmaceutical composition comprising 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51). The specification discloses that transplantation of corneas from Lewis strain rats to Wistar-Furth recipients, where rats receiving only vehicle demonstrate evidence of graft rejection, on average, at day 30. In contrast, in animals receiving MAE87, MAE106 or MAZ51 exhibit increased mean graft survival as demonstrated by a significant delay in evidence of graft rejection.

The specification does not teach how to make any and all "indolinone VEGFR-3 kinase inhibitor" and any "VEGFR-3 kinase inhibitor" that binds to theVEGFR-3 catalytic domain without the chemical structure and/or amino acid sequence that correlated with the functions for the claimed method of extending corneal graft survival following corneal transplantation in a human. The specification does not teach how to make any inhibitor mentioned above because there is insufficient guidance with respect to the structure without the amino acid sequence, or

chemical structure of *all* "VEGFR-3 kinase inhibitor" such as *all* "ATP analog", or *any* "VEGFR-3 inhibitor drown regulates VEGFR-3 expression", *any* "anti-angiogenic agent", or *any* "immunosuppressive agent", let alone which undisclosed ATP analog would bind to VEGFR-3 catalytic domain and function to inhibit lymphangiogenesis, and thereby extending corneal graft survival. Even if the inhibitor binds to VEGFR-3, binding does not equal to inhibiting lymphangiogenesis, in turn, useful for extending corneal graft survival. Likewise, inhibiting VEGFR-3 expression does not equal to extending corneal graft survival without sufficient working example. Even if the inhibitor binds to VEGFR-3, binding does not necessary mean down regulating VEGFR-3 expression.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Given the unlimited number of undisclosed indolinone VEGFR-3 kinase inhibitor, VEGFR-3 kinase inhibitor that binds to the VEGFR-3 catalytic domain, anti-angiogenic agent, and immunosuppressive agent, there is insufficient in vivo working example demonstrating the efficacy of the claimed method. Given the unlimited number of undisclosed indolinone VEGFR-3 kinase inhibitor, VEGFR-3 kinase inhibitor that binds to the VEGFR-3 catalytic domain, anti-angiogenic agent, and immunosuppressive agent and without the structure, it is unpredictable which undisclosed indolinone VEGFR-3 kinase inhibitor in combination with which undisclosed anti-angiogenic agent and/or immunosuppressive agent is effective for the claimed method. Until the indolinone VEGFR-3 receptor kinase inhibitor and anti-angiogenic agent or immunosuppressive agent have been identified, the specification as filed merely invites one of skill in the art for further experimentation to arrive at the scope of the claimed invention.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/7/05 have been fully considered but are not found persuasive.

Applicants' position is that the Office action acknowledged for the specific kinase inhibitors and such specific kinase inhibitors are disclosed on page 55, lines 17-32, and Table, page 56 of the specification. Claims 8-10, 15 and 26-38 have been canceled. The new claims 39-57 are directed to methods of extending corneal graft survival using the specific indolinones.

In response, claims 39-40 and 45-57 encompass methods of extending corneal graft survival using (1) *any* "VEGFR-3 kinase inhibitor", whereby lymphagiongenesis is suppressed in the cornea of said patient, (2) *any* VEGFR-3 kinase inhibitor" that binds to theVEGFR-3 catalytic domain, (3) the said method further comprises administering any anti-angiogenic agent, and/or (4) *any* immunosuppressive agent. The specification discloses only three VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structures as shown on page 56 and a method of extending corneal graft survival in a rat model of karetoplasty following corneal transplantation by administering a pharmaceutical composition comprising 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51). The specification discloses that transplantation of corneas from Lewis strain rats to Wistar-Furth recipients, where rats receiving only vehicle demonstrate evidence of graft rejection, on average, at day 30. In contrast, in animals receiving MAE87, MAE106 or MAZ51 exhibit increased mean graft survival as demonstrated by a significant delay in evidence of graft rejection.

The specification does not teach how to make any and all "indolinone VEGFR-3 kinase inhibitor" and any "VEGFR-3 kinase inhibitor" that binds to theVEGFR-3 catalytic domain without the chemical structure and/or amino acid sequence that correlated with the functions for the claimed method of extending corneal graft survival following corneal transplantation in a human. The specification does not teach how to make any inhibitor mentioned above because

there is insufficient guidance with respect to the structure without the amino acid sequence, or chemical structure of *all* "VEGFR-3 kinase inhibitor" such as *all* "ATP analog", or *any* "VEGFR-3 inhibitor drown regulates VEGFR-3 expression", *any* "anti-angiogenic agent", or *any* "immunosuppressive agent", let alone which undisclosed ATP analog would bind to VEGFR-3 catalytic domain and function to inhibit lymphangiogenesis, and thereby extending corneal graft survival. Even if the inhibitor binds to VEGFR-3, binding does not equal to inhibiting lymphangiogenesis, in turn, useful for extending corneal graft survival. Likewise, inhibiting VEGFR-3 expression does not equal to extending corneal graft survival without sufficient working example. Even if the inhibitor binds to VEGFR-3, binding does not necessary mean down regulating VEGFR-3 expression. Given the unlimited number of undisclosed indolinone VEGFR-3 kinase inhibitor, VEGFR-3 kinase inhibitor that binds to the VEGFR-3 catalytic domain, anti-angiogenic agent, and immunosuppressive agent, there is insufficient in vivo working example demonstrating the efficacy of the claimed method. Given the unlimited number of undisclosed indolinone VEGFR-3 kinase inhibitor, VEGFR-3 kinase inhibitor that binds to the VEGFR-3 catalytic domain, anti-angiogenic agent, and immunosuppressive agent and without the structure, it is unpredictable which undisclosed indolinone VEGFR-3 kinase inhibitor in combination with which undisclosed anti-angiogenic agent and/or immunosuppressive agent is effective for the claimed method. Until the indolinone VEGFR-3 receptor kinase inhibitor and anti-angiogenic agent or immunosuppressive agent have been identified, the specification as filed merely invites one of skill in the art for further experimentation to arrive at the scope of the claimed invention.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

7. Claims 39-40 and 45-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* and *all* "indolinone VEGFR-3 kinase inhibitor", whereby lymphagiongenesis is suppressed in the cornea of said patient, (2) *any* "VEGFR-3 kinase inhibitor" that binds to theVEGFR-3 catalytic domain,

(3) the said method further comprises administering any anti-angiogenic agent, and/or (4) any immunosuppressive agent for the claimed method as set forth in claims 39-40 and 45-57.

The specification discloses only three VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structure as shown on page 56 and a method of extending corneal graft survival in a rat model of karetenoplasty following corneal transplantation by administering a pharmaceutical composition comprising 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) that extends corneal graft survival in rat.

The specification defines the term "VEGFR-3 kinase inhibitor" means an inhibitor of receptor tyrosine kinase that selectively or non-selectively reduces the tyrosine kinase of a VEGF-3 receptor such as an inhibitor that reduces VEGFR-3 tyrosine kinase activity without significantly effecting VEGFR-3 expression or other VEGFR-3 activity (page 20). The VEGFR-3 kinase inhibitor can be *any* molecule that directly binds the VEGFR-3 catalytic domain, such as ATP analog. However, binding does not equal to function. Without a clear and adequate description about the structure associated with function of the genus of indolinone VEGFR-3 kinase inhibitor, VEGFR-3 kinase inhibitor, anti-angiogenic agent and immunosuppressive agent, the method of using a genus of VEGFR-3 kinase inhibitor, anti-angiogenic agent and/or immunosuppressive agent is not adequately described.

The specification discloses only three specific VEGFR-3 kinase inhibitors that extend corneal graft rejection, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of VEGFR-3 kinase inhibitor, anti-angiogenic agent and/or immunosuppressive agent to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 7/7/05 have been fully considered but are not found persuasive.

Applicants' position is that Claims 8-10, 15 and 26-38 have been canceled. New claims 39-57 are directed to methods of extending corneal graft survival using the specific indolinones.

In response, claims 39-40 and 45-57 encompass methods of extending corneal graft survival using (1) *any* "VEGFR-3 kinase inhibitor", whereby lymphagiongenesis is suppressed in the cornea of said patient, (2) *any* VEGFR-3 kinase inhibitor" that binds to theVEGFR-3 catalytic domain, (3) the said method further comprises administering any anti-angiogenic agent, and/or (4) *any* immunosuppressive agent.

The specification does not reasonably provide a **written description** of (1) *any* and *all* "indolinone VEGFR-3 kinase inhibitor", whereby lymphagiongenesis is suppressed in the cornea of said patient, (2) *any* "VEGFR-3 kinase inhibitor" that binds to theVEGFR-3 catalytic domain, (3) the said method further comprises administering any anti-angiogenic agent, and/or (4) any immunosuppressive agent for the claimed method as set forth in claims 39-40 and 45-57.

The specification discloses only three VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structure as shown on page 56 and a method of extending corneal graft survival in a rat model of karetenoplasty following corneal transplantation by administering a pharmaceutical composition comprising 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) that extends corneal graft survival in rat.

The specification defines the term "VEGFR-3 kinase inhibitor" means an inhibitor of receptor tyrosine kinase that selectively or non-selectively reduces the tyrosine kinase of a VEGF-3 receptor such as an inhibitor that reduces VEGFR-3 tyrosine kinase activity without significantly effecting VEGFR-3 expression or other VEGFR-3 activity (page 20). The VEGFR-3 kinase inhibitor can be *any* molecule that directly binds the VEGFR-3 catalytic domain, such as ATP analog. However, binding does not equal to function. Without a clear and adequate description about the structure associated with function of the genus of indolinone VEGFR-3 kinase inhibitor, VEGFR-3 kinase inhibitor, anti-angiogenic agent and immunosuppressive agent, the method of using a genus of VEGFR-3 kinase inhibitor, anti-angiogenic agent and/or immunosuppressive agent is not adequately described.

The specification discloses only three specific VEGFR-3 kinase inhibitors that extend corneal graft rejection, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of VEGFR-3 kinase inhibitor, anti-angiogenic agent and/or immunosuppressive agent to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. Claims 41-44 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

11. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner
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August 19, 2005

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